Allergic Implications of Blood Disorders in Infancy and Childhood

CARL H. SMITH, *M.D.*, New York City

• **The clinical manifestations of many of the blood disorders are wholly or partially dependent on immunoallergic reactions. A growing body of evidence permits the characterization of antigen-antibody mechanisms in connection with hemolytic anemia, purpura and agranulocytosis, and more specifically for each of the blood cell elements and for the vessel wall.**

These reactions extend to maternal-fetal relationships producing well defined blood disorders manifest at birth or in the neonatal period.

Once the effects of the hypersensitive state are set in motion during the course of a blood disorder, therapeutic measures to slow their progress are often futile. Because it is not always possible to identify the potentially allergic child in whom these circumstances will occur, it is extremely important to weigh the advantages of the use of a drug before it is administered especially when its side effects have not yet been thoroughly investigated.

Important information has recently been obtained regarding the heightened susceptibility to infection in children with chronic anemia who have had splenectomy to reduce the frequency of transfusions. The hypersensitive responses in children with spleen removed may result in overwhelming and often fulminating infections necessitating rigid criteria in selecting patients of the pediatric age for this operation.

THE ROLE OF HYPERSENSITIVITY in the pathogenesis of blood disorders depends upon the latitude given to this concept. Historically, allergy implies an altered capacity of the body to react to a foreign substance after repeated contacts with it. It denotes an intense and occasionally explosive reaction following the introduction of a substance innocuous in normal persons.

The type of response resulting from the combination of an antigen with an antibody has its counterpart in the immunoallergic mechanisms underlying many of the blood disorders. Many of these are now classified in that section of hematology designated as immunohematology and include hemolytic anemia, granulocytopenia and thrombocytopenia based on antibodies to the respective formed blood elements, blood vessel hypersensitivity, blood disorders resulting from incompatibility between blood elements of fetus and mother, transfusion reactions, and sensitivity induced by bacterial, chemical and physical agents.

In many instances a recognizable antigen-antibody mechanism can be determined; in others a hypersensitive state is inferred from the clinical features while still awaiting precise immunological identification. Frequently the manifestations of the blood disorder occur solely as a consequence of an antigen-antibody reaction. In other cases the disorder is a manifestation of an underlying disease. Thus autoimmune acquired hemolytic anemia in which the antibody is capable of reacting with the subject's own red cells to cause accelerated blood destruction may exist as a disease *sui generis* or occur in association with leukemia, disseminated lupus erythematosus, lymphosarcoma and other neoplastic diseases.

In this connection it is pertinent to dilate on the extraordinary phenomenon by which antibodies are elaborated which are capable of reacting with the patient's own red cells. A similar situation pertains in those cases of thrombocytopenic purpura and agranulocytosis in which antibodies are directed against the patient's platelets and polymorphonuclear cells. These disorders call attention to the remarkable tolerance developed from early fetal life by which the body in health avoids forming antibodies against its own tissues.[1] Such dire circumstances in which a living organism becomes capable of producing antibodies against its own body constituents, Ehrlich[2] termed "horror autotoxicus." The fundamental feature of autoimmune acquired hemolytic anemia and of other disorders characterized by autoimmune antibodies to blood cell elements is the loss of this normally acquired tolerance with the development of antibodies to one's own cellular antigens.

Although the blood disorders to be discussed in this paper represent a small segment of those encountered in pediatric practice, they illustrate the varied expressions of clinical disease when an allergic component is either partially or wholly responsible for their pathogenesis. Emphasis upon allergy

From the Department of Pediatrics, the New York Hospital-Cornell Medical Center, New York 21, N. Y.

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TABLE 1.—*Causes of Eosinophilia in Infancy and Childhood*

Allergic disorders: Bronchial asthma, hay fever, urticaria.

Skin diseases: Eczema, psoriasis, scabies and erythema neonatorum.

Parasitic infections: Trichinosis, Ascaris, echinococcus disease and visceral larva migrans.

Pulmonary eosinophilia: Eosinophilic pneumonitis (Loeffler's syndrome), prolonged pulmonary eosinophilia, tropical eosinophilia, pulmonary eosinophilia with asthma.

Blood disorders: Eosinophilic leukemia, Hodgkin's disease, following splenectomy, recovery phase of acute infectious lymphocytosis.

Irradiation.

Familial eosinophilia.

Miscellaneous infections and disorders: Scarlet fever, chorea; drugs and chemicals; benzol poisoning, camphor, phosphorus etc., periarteritis nodosa and metastatic neoplasms.

in no way indicates that this aspect represents the sole feature in every disorder in the arbitrarily selected group.

Eosinophilia

From the time when it was first demonstrated that foreign materials such as parasitic extracts were chemotactic for eosinophils, the relationship of these cells to diseases of sensitization has been amply confirmed. The number and proportion of eosinophils are greatly increased in patients with various types of allergic sensitivity, with parasitic infection, especially by nematodes, and following anaphylactic reactions. The eosinophil is the only cell which is known to respond specifically during states of hypersensitivity to become attached to shock tissues.[3] Since eosinophilic granulocytes appear in large numbers in conditions in which antigen-antibody reactions occur, the entities in which they are prominent may be reviewed. Accordingly those conditions are listed which are characterized by eosinophilia (Table 1). This will be taken to mean an increase of those cells above 5 per cent or 500 per cu. mm.

The recent case of a boy 9 years of age with leukocytes numbering 88,000 per cu. mm. of blood (80 per cent eosinophils) in association with diffuse parenchymal infiltration of both lungs, a hacking cough, eosinophil-laden sputum and intermittent fever, prompted a review of the causes of eosinophilia. In this patient the continous contact with a cat suggested a diagnosis of infection with *toxocara cata*.[4,5] In the absence of liver biopsy to demonstrate larvae a diagnosis of this condition could still be considered from the presence of the persistent and pronounced eosinophilia, pulmonary infiltration and moderate hepatomegaly.

An alternate diagnosis was one of the syndromes in which pulmonary involvement is accompanied by eosinophilia such as Loeffler's syndrome and prolonged pulmonary eosinophilia described by Crofton.[6] Of the two, prolonged pulmonary eosinophilia seemed the more likely by virtue of the persistence and extent of abnormal radiographic shadows and by the more intense degree of eosinophilia. In this case steroids (prednisone) produced a regression of the lung infiltration with symptomatic relief, and a reduction of leukocytes to 6,000 per cu. mm., 9 per cent eosinophils. However, the remission was short and the child eventually died of eosinophilic leukemia. The cells maintained their maturity until the last weeks of the course, at which time eosinophilic myelocytes appeared in the peripheral blood and bone marrow. The hemoglobin and red cell levels remained normal until the terminal phase of the illness.

An outline of the blood disorders in which immunoallergic mechanisms are operative is shown in Table 2. This concept is schematically represented in Chart 1.

TABLE 2.—*Blood Disorders in Infancy and Childhood Related to Immunoallergic Mechanisms*

1. Affecting blood cell and vascular elements:
   - A. Red cells:
     - Acquired hemolytic anemia:
       1. Toxic products, drugs, favism
       2. Antibodies against red cells
          - (a) Erythroblastosis fetalis
          - (b) Blood transfusion reactions
          - (c) Associated with autoantibodies
            Primary—Autoimmune hemolytic anemia
            Secondary—Leukemia, Gaucher's disease
          - (d) Pure red-cell (chronic congenital aregenerative) anemia?
   - B. White blood cells:
     - Agranulocytosis:
       1. Anticonvulsants
       2. Antimicrobial agents
       3. Antithyroid drugs
       4. Sulfonamides
     - Neonatal agranulocytosis
   - C. Platelets:
     - Thrombocytopenic purpura:
       1. Idiopathic
       2. Congenital
       3. Drug-induced: Quinine, quinidine, sulfonamides, arsenicals
       4. Eczema with purpura and otitis media
   - D. Red cells, white cells and platelets:
     - Hypoplastic and aplastic anemia:
       1. Idiopathic
       2. Drugs, chemicals, infection
   - E. Blood vessels:
     - Allergic purpura (Henoch-Schönlein syndrome)
     - Idiopathic pulmonary hemosiderosis
     - Polyarteritis nodosa and other collagen diseases
     - Thrombotic thrombocytopenic purpura (vascular vessel wall in combination with platelets and red cells).
2. Infections: Infectious mononucleosis, susceptibility following splenectomy.

Chart 1.—Immunoallergic Concept of Blood Disorders

Causative Factors		
Infection, Foods, Drugs, Chemicals, Unknown or suspected	Antibodies	Red cell: Autoimmune hemolytic disease
		White cell: Agranulocytosis, L.E. phenomenon
		Platelets: Idiopathic thrombocytopenic purpura
		Erythrocytes, leukocytes, platelets: Aplastic anemia
		Vessel walls: Henoch-Schönlein purpura
		Vessel wall, erythrocytes, platelets: Thrombotic thrombocytopenic purpura

Pure Red-Cell Anemia (Chronic Congenital Aregenerative Anemia)

Since from an anatomic point of view the maternal and fetal circulations are separated by only two layers of cells, placental transmission of a variety of substances including maternal antibodies, isoagglutinins, and plasma proteins is facilitated in human infants. In addition, serological and biologic evidence has been presented of transplacental transfusions of blood from the baby to the mother through small or gross defects in the placenta. This passage of fetal red blood cells into the maternal circulation through breaks of varying size in the placental barrier accounts for the method by which an Rh-negative woman is sensitized by an Rh-positive fetus. A or B agglutinogens as well as other antigenic substances can similarly be transmitted into the maternal circulation with the production of antibodies to react with appropriate fetal elements.[7]

In addition to the well known effects of isoimmunization in erythroblastosis, other blood disorders may also occur whose pathogenesis can be traced to the passage of agglutinins across the placental barrier. In a case under our observation[7] the onset of anemia dated from the newborn period with the clinical and hematological feature of mild erythroblastosis fetalis. The mother's blood group was O, Rh-positive, and that of the infant and the father was A, Rh-positive. The anti-A serum titer in the mother reached a maximum of 1:128,000. The bone marrow revealed a persistent depression of erythropoiesis but the platelet and granulocyte levels were entirely unaffected resulting in refractory anemia. This blood condition persisted over a period of ten years, the lifetime of the child, in spite of frequent transfusions, use of steroids and a variety of other treatments designed to stimulate erythrogenesis. It was postulated that prolonged depression in red cell production resulted from an antibody directed against the red cells in fetal life and the early neonatal period. In this case the sensitivity of the mother to A agglutinogen was extreme. It should be emphasized that this concept is offered to explain the mechanism of the anemia in this case and does not provide a uniform explanation for the pathogenesis of all cases of this disease.

Autoimmune Acquired Hemolytic Anemia

In addition to cases of acquired hemolytic anemia in which the cause is identified are those cases for which no recognizable cause can be found. These are autoimmune hemolytic anemia due to an unknown mechanism whereby the body produces antibodies against its own red blood cells.

The disease may be acute, self-limited and occasionally fulminating, or chronic and marked by repeated attacks of hemolysis followed by remissions. Frequently the chronic case is marked by insidious onset with a subsequent course of increasing severity. Clinically it is important to separate the primary and idiopathic cases from the secondary or symptomatic cases in which hemolysis is a complication of an underlying disease.

The serum of a patient with both idiopathic and symptomatic acquired hemolytic anemia will generally be found to possess an abnormal red cell antibody which attacks not only the red cells of the patient, but also red cells of blood from normal persons. With rare exceptions the presence of antibody adsorbed on the patient's red cells is detected by finding a positive direct antiglobulin or Coomb's test. A positive Coomb's test in acquired hemolytic anemia in contrast to the negative test in hereditary spherocytosis is frequently helpful in differentiating the two conditions since spherocytosis and reticulocytosis occur in both.

Before the advent of corticotropin and steroid therapy, great reliance was placed on splenectomy for treatment of chronic idiopathic acquired hemolytic anemia. Results were, however, unpredictable; the operation was regarded as successful in approximately 50 per cent of the idiopathic cases, but for how long was not always certain. Since autoantibodies are produced in large measure by the spleen, the removal of this organ should be expected to result in a sharp decrease in their concentration. The variable effect of splenectomy in many cases indicates, however, that the spleen may not be the sole source of antibody. In some cases the antibody titer decreases sharply after splenectomy and in other cases improvement results even with a high titer of antibody.

Idiopathic Thrombocytopenic Purpura

Idiopathic thrombocytopenic purpura (ITP) is a disease of unknown cause that is characterized by a hemorrhagic tendency resulting from pronounced reduction in the number of blood platelets. It occurs in two major types, one an acute self-limited form,

and the other a chronic protracted disease with occasional remissions. Bone marrow examination will determine whether the purpura is secondary to leukemia or aplastic anemia. Banti's syndrome, Gaucher's disease, disseminated lupus erythematosus and other types of secondary hypersplenism are also to be considered.

Recent evidence demonstrating an immunologic mechanism in some cases of idiopathic thrombocytopenic purpura has stimulated interest in this disease and the treatment of it. Information from two sources suggested the possibility that an immunologic reaction might be involved in idiopathic thrombocytopenic purpura. The observation that infants born to mothers with idiopathic thrombocytopenic purpura often were purpuric was ascribed to the transmission of an immune body across the placenta. In addition Evans and co-workers[8,9] presented evidence for a relationship between acquired hemolytic anemia and primary thrombocytopenic purpura. They noted that acquired hemolytic anemia with sensitization of the red cells is often accompanied by thrombocytopenia, and that primary thrombocytopenia is frequently accompanied by red cell sensitization with or without hemolytic anemia. Since acquired hemolytic anemia had been shown to be due to an autoantibody these investigators suggested that primary thrombocytopenic purpura was due to a thrombocyte autoantibody.

Harrington and co-workers[10] demonstrated that an immunologic mechanism was responsible for the low platelet count in many cases of idiopathic thrombocytopenic purpura. Platelet agglutinins were demonstrated in vitro in the plasma of many patients with thrombocytopenia of the idiopathic variety. A factor presumably identical to this platelet agglutinin is capable of inducing thrombocytopenic purpura and altering megakaryocytes in normal recipients of this plasma. The spleen is therefore involved in removing sensitized platelets and of producing platelet agglutinins in variable amounts. Some of the antibody is made in the spleen, the major portion elsewhere. In spite of the evidence that idiopathic thrombocytopenic purpura is based on an immunological mechanism, circulating platelet antibodies have not universally been found with standard procedures.

The pathogenesis of purpura due to drug idiosyncrasy provides information of an immunological nature which is applicable to the causation by other types of offending agents. The fact that drugs such as Sedormid (allyl-isopropyl-acetylcarbamide) neoarsphenamine and quinine can on occasion produce either thrombocytopenic or nonthrombocytopenic purpura led Ackroyd[11] to postulate that the two phenomena are independent, that purpura is essentially a vascular lesion and that thrombocytopenia when present tends to increase the hemorrhagic tendency.

The addition of Sedormid to the platelets suspended in the serum of a sensitized patient causes agglutination of them without complement, and lysis with it. Patients who have recovered from Sedormid purpura possess an antiplatelet antibody in the circulating blood which is capable of destroying platelets. The fact that normal serum had no such effect indicates that the abnormality in the blood of such a person lies in the serum and not in the platelets. In thrombocytopenic purpura due to Sedormid (and probably to other drugs) the antibody acts on megakaryocytes, platelets and capillary endothelium. In nonthrombocytopenic purpura the platelets for some unknown reason escape injury. The drug presumably combines with vascular endothelium rendered antigenic and therefore capable of uniting with antibody. Thrombocytopenia due to quinine presents a similar mechanism, the antigen to which antibody is produced as a complex composed of the union between the drug and platelets.[12]

Congenital Thrombocytopenic Purpura

Congenital thrombocytopenic purpura occurs infrequently but the literature contains many case reports and studies bearing on the pathogenesis.[13,14,15,16] It appears in infants born of mothers with idiopathic thrombocytopenic purpura who have either had a splenectomy or are symptomless and unaware of a lowered content of platelets, in infants born of normal mothers and in infants of mothers with drug-induced thrombocytopenic purpura such as follows the ingestion of quinine.

Current concepts implicate an immunoallergic mechanism in the causation of the disease in infants. According to Harrington[17] one-third of the mothers do not have any demonstrable autoantibodies for platelets and are assumed to have a defect of platelet formation from megakaryocytes as the sole factor causing thrombocytopenia. Mothers with idiopathic thrombocytopenia of this type give birth to normal infants. On the other hand patients with autoimmune idiopathic thrombocytopenic purpura possess a circulating antibody which damages both platelets and megakaryocytes. Mothers with this variety of thrombocytopenia give birth to purpuric infants. The antibodies which cross the placenta into the fetal circulation consist of autoagglutinins for the platelets of the mother and infant as well as isoagglutinins for each other's platelets.

In the case of a normal mother it has been postulated that she develops isoagglutinins for the baby's platelets, presumably on the basis of platelet incompatibility between mother and infant in a manner analogous to Rh-sensitization in erythroblastosis. She may also have been sensitized to platelet antigen

in a previous transfusion or to fetal platelets of a different antigenic composition during pregnancy. The precise nature of the immune substance is not always obvious.

Agranulocytosis

In leukopenic syndromes, substances acting upon leukocytes have been detected which are comparable to the antibodies present in the sera of patients with thrombocytopenia and acquired hemolytic anemias. Moeschlin and Wagner[18] demonstrated, in a case of agranulocytic angina, leukocyte-destroying factors in the serum which were active in vivo and in vitro. Drugs such as aminopyrine combine with a protein in the serum, forming an antigen which causes sensitization with antibody formation. The antibody becomes attached to the leukocytes which are agglutinated and destroyed when they come in contact with the antigen.[19] Not only does the serum of such a patient agglutinate normal human leukocytes in vitro, but injections into a normal person causes a rapid decrease in the number of leukocytes. The destruction of agglutinated leukocytes probably occurs in vivo in the lung capillaries.[20]

Neonatal Agranulocytosis

Lubhy and Slobody[21] observed transient agranulocytosis in successive siblings in the neonatal period. Such a circumstance was explained by transplacental isoimmunization of the mother to a leukocyte factor of her infant in a manner analogous to Rh isoimmunization causing hemolytic disease of the newborn. In these cases agranulocytosis persisted for three to four weeks and in one of the infants it was accompanied by pulmonary infection. The predominance of neutrophilic myelocytes in the bone marrow may represent either a maturation arrest or a depletion of mature cells because of their increased agglutination and destruction in the peripheral blood.[21]

Idiopathic Pulmonary Hemosiderosis

Idiopathic pulmonary hemosiderosis is a rare disease usually occurring in childhood and in young adults and characterized by dyspnea, cyanosis, fever, cough, fatigability and anemia. The development of severe anemia in a child during repeated attacks of bronchopulmonary infection should call attention to this disease. Terminal cardiorespiratory failure resulting from the effects of recurrent pulmonary bleeding is a frequent but not invariable outcome. The course is one of remissions and exacerbations with intermittent hemoptysis and hematemesis accompanied by moderate to severe anemia with acute episodes lasting two to three days but occasionally persisting for several weeks.[22,23,24,25,26]

The disease has been ascribed to a primary developmental defect of the elastic fibers, with fragmentation of them resulting in stasis of capillary vessels and hemorrhages. The failure to find destruction of elastic tissue in all cases led Steiner[27] to regard essential pulmonary hemosiderosis as an antigen-antibody reaction caused by a still unknown sensitizing agent inducing the production of autoantibodies. With the lungs as a shock organ the antigen-antibody reaction produces capillary dilation, stasis, diapedesis, rhexis and increased destruction of red corpuscles and deposits of hemosiderin.

On the basis of this immunoallergic hypothesis, steroids and corticotropin (ACTH) have been advocated. Favorable reports with this treatment require further evaluation of more extended experience because of the great variations in the frequency and severity of attacks. For the effects of acute loss of blood into the lung, transfusions, rest in bed and administration of iron are required.

Allergic Purpura (Anaphylactoid Purpura, Henoch-Schonlein Purpura)

Allergic purpura refers to a type of nonthrombocytopenic purpura accompanied by a pleomorphic and usually purpuric type of cutaneous eruption in combination with gastrointestinal symptoms (Henoch's purpura), painful swelling of the joints (Schönlein's purpura rheumatica) and a tendency to renal involvement. These features are grouped together as the Henoch-Schönlein syndrome with the realization that these symptom complexes can occur individually, in combination or in sequence.

The relationship of the purpuric state to allergic sensitivity is suggested by the symptoms of urticaria, diffuse erythema, subcutaneous and submucous extravasations of blood and lymph. While hypersensitivity is generally considered to underlie the Henoch-Schönlein syndrome, a definite allergen is only rarely identified. Food and, less frequently, bacterial infection and drugs including antibiotics, are suspected as the exciting factors. A large variety of foods have been implicated, chiefly eggs, milk, chocolate, wheat, nuts and beans and to a lesser extent fish, pork, lamb, chicken and a variety of fruits.[11] In one case an insect bite led to swelling of joints, blood-tinged stools and hematuria.[28] While a relationship is suggested clinically, results of skin tests are generally negative and more is gained by eliminating the suspected foods from the diet and observing for the subsidence of symptoms. The high incidence of preceding upper respiratory infections often with beta-hemolytic streptococci and the similarity between the latent period of one to three weeks until the appearance of the hemorrhagic manifestations suggest both a close association between Henoch-Schönlein purpura and acute nephritis, and the hyperimmune nature of both diseases.

A disturbance of the vascular endothelium resulting in increased capillary fragility and permeability is a basic factor in the symptomatology. Osler[29] was

among the first to call attention to the association between arthritis and intestinal symptoms and the erythema group of skin diseases and to emphasize the renal complications.

The Henoch-Schönlein syndrome has been linked[30] with acute nephritis, rheumatic fever and polyarteritis nodosa and other members of the group of collagen diseases. They have overlapping clinical characteristics and a similar pathogenesis based on an antigen-antibody reaction involving the endothelium of blood vessels. The Henoch-Schönlein purpura can thus be classified as an immuno-vascular disorder resulting in a generalized blood vessel disturbance or angiitis affecting the skin, joints, intestinal tract and renal glomeruli.[31]

An antiserum made experimentally from vascular endothelium has been found to produce diffuse hemorrhagic purpura in the skin and internal organs. Following the direction of previous Japanese investigators, Clark and Jacobs,[32] using suspensions of dog vascular endothelium from the aorta and vena cava, produced a rabbit antiserum which when injected into dogs produced generalized nonthrombocytopenic hemorrhagic purpura. The resulting lesions corresponded to the diffuse vasculitis involving small blood vessels with perivascular collections of polymorphonuclear cells, lymphocytes and macrophages observed in Henoch-Schönlein disease. These changes provide a basis for the increased permeability of small blood vessels. An infection, drugs or toxin for example may form a complex with capillary endothelium or platelets along the lines suggested by Ackroyd,[11] with Sedormid therapy thus initiating active immunization. Further confirmation of the concept of Henoch-Schönlein disease as a hyperimmune disease was the application of a precipitin test using a preparation of the aorta of newborn infants. A positive result of a precipitin test with decalcified serum was obtained in six of eight cases of allergic purpura and in three of four cases of periarteritis nodosa.[33]

The L.E. Phenomenon: Relation to Immunologic Mechanisms

The factor responsible for the L.E. phenomenon in patients with disseminated lupus erythematosus is associated with the gamma globulin fraction of the plasma. A generally accepted theory of L.E. cell formation is that the L.E. plasma factor induces specific chemical changes in leukocytic nuclei, the depolymerization of desoxyribose nucleic acid, and that these altered nuclei are later ingested by other leukocytes to form L.E. cells. An alternate theory explains nucleophagocytosis on the basis of antinuclear autoantibodies. That an immunologic mechanism may be responsible for the nucleophagocytosis of the L.E. phenomenon is suggested by the associated evidences of autoimmune hemolytic anemia and of thrombocytopenia in this disease, and the experimental production in vitro of L.E. cells.[34] Nucleophagocytosis produced experimentally by mixing antileukocytic serum with leukocytes from the same source resulted in structures resembling L.E. cells.[35] According to this hypothesis the L.E. plasma factor constitutes an "autoimmune" substance which stimulates antileukocyte antibody. In the presence of the L.E. factor white cells are sensitized and phagocytized by other leukocytes[36] and a high antibody serum would be responsible for both the ultimate development of L.E. cell and the formation of rosettes.[37]

Thrombotic Thrombocytopenic Purpura

Thrombotic thrombocytopenic purpura is an acute febrile disease characterized by thrombocytopenic purpura, severe hemolytic anemia and transitory focal neurologic signs. The varied symptoms and signs are due to widespread intracapillary and intraarteriolar thrombi affecting most frequently the brain, kidneys, heart and spleen. The occlusions are not due to agglutinated platelets alone but to the vascular wall involvement with conspicuous endothelial proliferation.

It has been postulated that thrombotic thrombocytopenic purpura represents an immunohematologic disorder in which the autoimmune process is set in motion against the red cells, platelets, megakaryocytes and vessel wall.[38] The association of pronounced eosinophilia in an occasional case[39] tends further to support this concept. The hypersensitive basis of the histologic picture is analogous to other collagen diseases particularly periarteritis nodosa and lupus erythematosus and to the necrotizing vascular lesions produced by Rich and co-workers[40] in experimental animals by a variety of agents such as foreign proteins, sulfonamides and iodine.

Susceptibility to Infection in Children with Splenectomy

A collateral aspect worthy of note is the susceptibility to infection in children who have had splenectomy. This aspect focuses attention on the spleen as an agent of immunity as has been abundantly demonstrated in experiments with animals.

Important information recently obtained[41] demonstrated the heightened susceptibility to infection in children with chronic anemia in whom the spleen had been removed in order to reduce the number of transfusions. The series consisted of a group of children with chronic hemolytic anemia, hypersplenism, chronic congenital aregenerative (pure red-cell) anemia and thrombocytopenic purpura, as well as two healthy children with traumatic rupture of the spleen.

The infections fell into several well defined clinical categories: Meningitis, fulminating infection and

sepsis, acute idiopathic pericarditis (confined to Cooley's anemia) and acute bacterial endocarditis. In instances in which bacterial diagnosis was possible, the pneumococcus was the most common offender with meningitis the most frequent clinical type of infection.

What was conspicuous was the frequency of serious infection in these children as compared with its relative paucity in adults with splenectomy. In 225 consecutive adult patients (over 20 years of age) in The New York Hospital who had had the spleen removed, only one serious infection occurred, namely, pneumococcic meningitis one month after splenectomy for acquired hemolytic anemia. This experience is in sharp contrast with 14 cases of severe infection in 50 children without a spleen in the same institution, an incidence of 28 per cent. Four patients in the latter group (8 per cent) died in the particular episode of fulminating infection. It should be emphasized that in a group of comparable patients with severe Cooley's anemia and intact spleen, infections of the nature described did not occur. The relation of age of the subject to susceptibility to infection is an intriguing one. The concept of "serological maturity" has been postulated[42] to emphasize both exposure to latent or subclinical infections in childhood and the physiologic changes relating to the acquisition of resistance coincidental with increasing years and not related to previous infection.

These untoward circumstances in children deprived of the spleen suggest more than a fortuitous association between splenectomy and susceptibility to infection, which prompts renewed consideration of the role of this organ in the defense mechanisms of the body. While the number of cases of this complication is small in comparison with the ever increasing number of cases of splenectomy, the potential hazards demand that exact criteria be established in selecting patients of the pediatric age for the operation. While it is impractical to keep children with splenectomy under observation for prolonged periods, close supervision for at least two years after operation—the period of most frequent incidence of infection—becomes obligatory.

525 East 68th Street, New York 21, N. Y.

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